

# The Inverse Aspect of Metaheuristics for the Parameter Identification of S-systems

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## Abstract

The genetic regulatory network, which is constructed from the time-courses data sets, is always described as highly nonlinear differential equations. Mathematical and computational modeling technologies focus on efficiently identifying the parameters of the nonlinear dynamic biological system. Various derivative-free and derivative-based optimization technologies have been proposed recently to infer the parameters of the S-type genetic regulatory networks (S-systems). The S-system is described as coupled power-law functions. As the involved genes and/or proteins increase, the identification becomes increasingly difficult; multiple attractors exist in the system. How to develop an optimization algorithm to reduce the computation time while keeping the accuracy is necessary. In this study, a gradient-based metaheuristics is proposed. The computational method starts with the hill-climbing optimization, and solves the stagnation phenomenon by using a differential climbing operation and migration synchronous evolution. This method was tested with four biological systems. To show the performance in the solution quality and the computation time, we let the learning be implemented in a wide search space ( $[0, 100]$  for rate constants and  $[-100, 100]$  for kinetic orders) and initialized all parameters at a bad point (the neighbourhood of 80).

## Keywords

*Parameter Estimation; S-System; Memetic Computation; Genetic Algorithm*

## Introduction

Data-driven modelling is a corner stone of systems biology (Vilela et al., 2008). Researchers have to model biological networks such that the regulatory interactions between the genes and/or proteins are identified. The S-system structure (Savageau, 1976; Voit, 2000) is a popular nonlinear model which is able to capture the dynamic behaviour of gene regulation networks, metabolic pathways or signal transduction cascades. This structure directly identifies the interaction between genes and/or proteins, and possesses good generalization characteristics.

However, the identification challenges researchers due to variables in multimodal distribution.

Wang et al. (2010) considered two extreme cases to determine the parameters' ranges and mean values. Xang et al. (2012) fixed the efflux function and determined the unknown parameters of the influx function through the slope error. Various derivative-free-based technologies have recently proposed. Cho et al. (2006) used genetic programming. Wang and collaborators (Liu and Wang, 2009; Wang and Liu, 2010) used hybrid differential evolution. Chen et al. (2010) hybridized genetic algorithm and simulated annealing. Xu et al. (2007) used the neural network with the particle swarm optimization.

Some researchers adopted derivative-based technologies to identify the S-systems' parameters. Marino and Voit (2006) proposed a step-by-step progress in model complexity. Chou et al. (2006) used alternative-regression methods. Vilela et al. (2008) used eigenvector methods. Kotalik et al. (2007) used Newton-flow methods. Sriyudthsak et al. (2013) introduced the Granger causality test to infer the structure and then used Levenberg-Marquardt algorithm to solve the unknown parameters. Chemmangattuvalappil et al. (2012) sequentially reduced the number of the unknown parameters and used least square optimization for parameter identification. However, the derivative-based optimization methods have the possibility of getting trapped into locally optimal points. The accuracy of these approaches depended too much upon both initially starting points and the degree of system's nonlinearity.

It is better to hybrid these two different approaches such that the explorative and exploitive abilities are increased simultaneously. Memetic algorithms (MAs) are the hybrid programs which incorporate local-search methods into global-search technologies. MAs are successful in solving various optimization

problems of other fields. Harman and McMinn (2010) empirically studied the performance of local and global search in MAs. Soh et al. (2010) proposed archiving molecular and basin-hopping algorithms to identify low-energy pure-water isomers. Ahn et al. (2010) designed an electromagnetic system. Meuth et al. (2009) made a review of Mas and proposed a high-order meta-learning system. Kramer (2010) proposed a Powell-ILS strategy. Tsoulos and Lagris (2008) hybridized these two in series. Yang and Jat (2011) proposed a guided-search scheme.

Most hybrid techniques used evolutionary algorithms to identify a suitable initial start for local-search learning. In this paper, we propose an inverse aspect: Integrate stochastic operations into the gradient-based optimization, instead of incorporating the latter into the former. This technology avoids from sticking in local minima by adjust the climbing direction and some stochastic operations. The proposed technology was tested with four biological systems. To further exhibit the exploration performance the learning was implemented in a wide search space ([0, 100] for rate constants and [-100, 100] for kinetic orders) with a bad initial start (all parameters were initially set to 80-neighborhood).

### Gradient-Based Metaheuristics Optimization

Based on biochemical system theory, the net influx ( $V_i^+$ ) and efflux ( $V_i^-$ ) of an S-system are approximated as power-law functions. The concentration change of a metabolite, protein or gene is expressed by Eq. (1) (Voit, 2000),

$$\dot{X}_i = V_i^+ - V_i^- = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}}, \quad (1)$$

for  $i=1,2,\dots,n$ , where  $n$  and  $m$  are the numbers of dependent and independent variables, respectively,  $\alpha_i$  and  $\beta_i$  are rate constants, and  $g_{ij}$  and  $h_{ij}$  are the kinetic orders that denote the interaction from  $X_j$  to  $X_i$ .

In order to construct such a highly dimensional nonlinear system, a gradient-based metaheuristics is proposed. The computational method starts with the hill-climbing optimizer, and solves the stagnation phenomena by both differential climbing operations and migration synchronous evolution. The former operation is to adjust the climbing direction and the latter is to widen the searching such that a valid escape is ensured. Fig. 1 is the proposed flowchart.

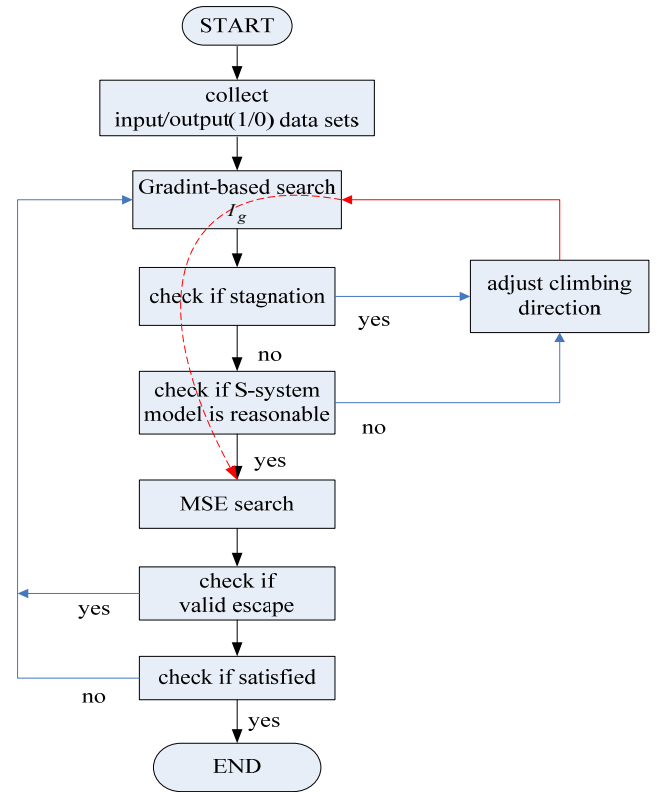


FIG. 1 THE FLOWCHART OF GRADIENT-BASED METAHEURISTICS OPTIMIZATION.

### Times Series Data

The time-courses data sets for training and testing were generated from the S-systems, which were cited from the published papers (Tsai and Wang, 2005; Kikuchi et al., 2003; Voit and Almeida, 2004), in different sets of initial conditions.

### Adjust Climbing Direction

The climbing direction is differentially adjusted toward individuals over the searching space:

$$I_g = I_g + r_1 * d_1 * (I_g - I_{r1}) + r_2 * d_2 * (I_g - I_{r2}), \quad (2)$$

where  $d_1$  and  $d_2$  denote the size of a step ( $d_1=d_2=1$  for our systems),  $r_1$  and  $r_2$  are random factors, and  $I_{r1}$  and  $I_{r2}$  are two randomly selected individuals.

### Migration Synchronous Evolution (MSE)

Real-value-coded genetic algorithm is used for the gradualness of the variables. We encode the unknown parameters of the S-system as a chromosome, and arrange all chromosomes in order according to their fitness values. The best individual  $I_b$  ( $=I_1$ ) has the smallest residual error.

#### 1) Synchronous Mutation

To ensure global searching, we introduce a

synchronous mutation operation. Instead of adopting only one gene (one-point mutation), two genes (two-point mutation), or a fixed number of genes (mask mutation) for mutation, we let all of the genes mutate with a probability that is assigned by the designer. Those genes with the mutation probability  $r_1$  over the randomly given threshold  $r_2$  are qualified to replace their original ones:

$$x_{ij} = \begin{cases} \hat{x}_{ij}, & \text{if } r_1 > r_2 \\ x_{ij}, & \text{otherwise} \end{cases} \quad (3)$$

where  $x_{ij}$  is the  $j$ th chromosomes in the  $i$ th individual, and  $r_1, r_2 \in [0, 1]$  are two random numbers. The synchronous-mutation operation brings the population sufficient diversity, but may induce a leak in hill-climbing. Therefore, the elitism strategy is introduced to compensate the leak. Elitism keeps the best-so-far individual to survive for each generation and ensures the best characteristic to pass down.

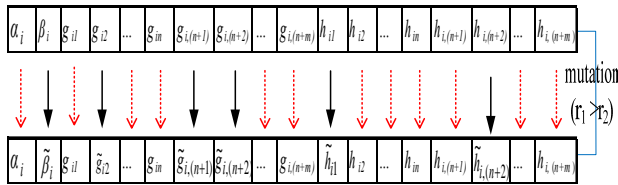


FIG. 2 SYNCHRONOUS MUTATION.

## 2) Migration

To achieve a wider search we further introduce the migration operator such that the new generated population covers the entire search space. The migration operation is executed in each iteration. After this operation new chromosomes are generated. The  $j$ th gene of the chromosome  $I_i$  is changed to

$$x_{ij} = \begin{cases} x_{bj} + r_2 \times (x_{j,\min} - x_{bj}), & \text{if } \lambda_b > r_1 \\ x_{bj} + r_2 \times (x_{j,\max} - x_{bj}), & \text{otherwise} \end{cases} \quad (4)$$

where  $\lambda_b = \frac{x_{bj} - x_{j,\min}}{x_{j,\max} - x_{j,\min}}$ ,  $x_{bj}$  are the  $j$ th gene of the

best chromosome,  $x_{j,\max}$  and  $x_{j,\min}$  are the upper and lower bound of the  $j$ th gene, respectively, and  $r_1, r_2 \in [0, 1]$  are two random numbers.

## Artificial Experiments and Discussion

In order to examine the performance of the proposed technology, we tested it with a three-gene cascade pathway (Tsai and Wang, 2005), a four-gene genetic-

branch pathway (Voit and Almeida, 2004), a five-gene small-scale genetic network (Kikuchi et al., 2003; Hlavacek and Savageau, 1996), and a medium-scale genetic network (twenty genes) (Noman and Iba, 2006). We initialized all parameters at the neighborhood of 80, and set the range of the rate constants as  $[0, 100]$  and that of the kinetic orders as  $[-100, 100]$ . All computations were performed on an Intel Core duo 3.16 GHz computer using Microsoft Windows XP. The performance is determined by the weighted mean-square error (residual error),

$$E = \frac{1}{N} \sum_{i=1}^N t_a \left( \frac{x^i - x_{\exp}^i}{\max(x_{\exp}^i)} \right)^2 \quad (5)$$

where  $x^i$  and  $x_{\exp}^i$ ,  $i=1, \dots, n$  are, respectively, the estimated concentration and artificial-measured concentration,  $t_a$  is a time-weighting factor, and  $N$  is the number of sampled data points. The cubic-spline technology was used to generate the smooth profile of the time-series data

## Cascade Pathway System

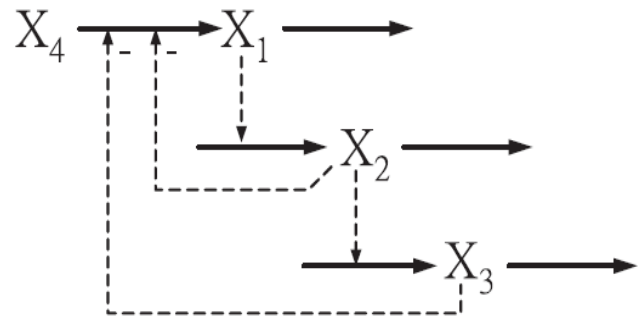


FIG. 3 A CASCADE PATHWAY (TSAI AND WANG, 2005)

We first consider the cascade pathway shown in Fig. 3 (Tsai and Wang, 2005). This is a three-step system with two feedback signals. The system has three dependent variables ( $x_1, x_2$  and  $x_3$ ) and one independent variable ( $x_4$ ). The respective S-system is

$$\begin{aligned} \dot{x}_1 &= \alpha_1 x_2^{g_{12}} x_3^{g_{13}} x_4 - \beta_1 x_1^{h_{11}}, \\ \dot{x}_2 &= \alpha_2 x_1^{g_{21}} - \beta_2 x_2^{h_{22}}, \\ \dot{x}_3 &= \alpha_3 x_2^{g_{32}} - \beta_3 x_3^{h_{33}}. \end{aligned} \quad (6)$$

The values of parameters are listed in Row “true” of Table 1. We generated eight-set artificially experimental concentration data for the training. The simulation time is 8 seconds, and the sampling time is 0.02. After the training, we get the estimated parameters, which are shown in Row “simulation” of

Table 1. The estimated residual error in Eq. (5) is 1.0591741E-10.

### Genetic-Branch Pathway System

The second system is the genetic-branch pathway in Fig. 4, which is used by Voit and Almeida (2004). The respective S-system is described as Eq. (7).

$$\begin{aligned} \dot{x}_1 &= \alpha_1 x_3^{g_{13}} x_0 - \beta_1 x_1^{h_{11}}, \\ \dot{x}_2 &= \alpha_2 x_1^{g_{21}} - \beta_2 x_2^{h_{22}}, \\ \dot{x}_3 &= \alpha_3 x_2^{g_{32}} - \beta_3 x_3^{h_{33}} x_4^{h_{34}}, \\ \dot{x}_4 &= \alpha_4 x_1^{g_{41}} - \beta_4 x_4^{h_{44}}. \end{aligned} \quad (7)$$

The system has four dependent variables ( $x_1, x_2, x_3$  and  $x_4$ ) and one independent variable ( $x_0$ ). Row "True" of Table 2 shows the parameters. Eight sets of

artificial experimental data ( $x_{\text{exp}}^i, i = 1, \dots, n$ ) are used for the training. The simulation time for each experiment is 8 seconds and the sample time is 0.02. Row "Simulation" of Table 2 shows the estimated parameters, all of which are nearly the same as their respective true values. The mean-square error in Eq. (5) is 2.2096583E-11.

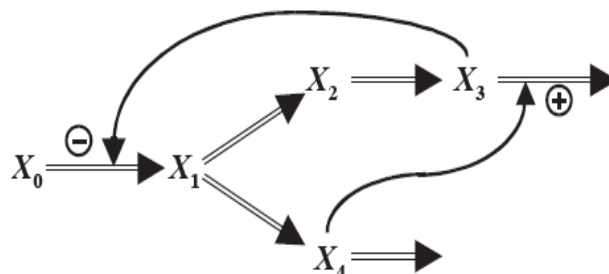


FIG. 4 A GENETIC-BRANCH PATHWAY (VOIT AND ALMEIDA, 2004).

TABLE 1 TRUE AND ESTIMATED PARAMETERS OF AN S-TYPE SYSTEM FOR A CASCADE PATHWAY (3 GENES) IN FIG. 3. ROW "TRUE" IS THE PARAMETERS OF A TRUE S-SYSTEM. ROW "SIMULATION" IS THE ESTIMATED PARAMETERS FOR A WIDE SEARCH SPACE ([0,100] FOR RATE CONSTANTS AND [-100, 100] FOR KINETIC ORDERS) WITH A BAD INITIAL START (80 FOR ALL PARAMETERS).

|            | variable | $\alpha_i$    | $\beta_j$     | $g_{i1}$      | $g_{i2}$       | $g_{i3}$       | $h_{i1}$      | $h_{i2}$      | $h_{i3}$      |
|------------|----------|---------------|---------------|---------------|----------------|----------------|---------------|---------------|---------------|
| true       | $x_1$    | 10            | 5             |               | -0.1           | -0.05          | 0.5           |               |               |
|            | $x_2$    | 2             | 1.44          | 0.5           |                |                |               | 0.5           |               |
|            | $x_3$    | 3             | 7.2           |               | 0.5            |                |               |               | 0.5           |
| simulation | $x_1$    | 9.9999645E+00 | 4.9999930E+00 |               | -9.9999021E-02 | -5.0001491E-02 | 5.0000005E-01 |               |               |
|            | $x_2$    | 2.0000463E+00 | 1.4400463E+00 | 4.9999122E-01 |                |                |               | 4.9998848E-01 |               |
|            | $x_3$    | 3.0002409E+00 | 7.2001110E+00 |               | 4.9996317E-01  |                |               |               | 4.9996313E-01 |

TABLE 2 TRUE AND ESTIMATED PARAMETERS OF AN S-TYPE SYSTEM FOR A GENETIC BRANCH PATHWAY (4 GENES) IN FIG. 4. ROW "TRUE" IS THE PARAMETERS OF A TRUE S-SYSTEM. ROW "SIMULATION" IS THE ESTIMATED PARAMETERS FOR A WIDE SEARCH SPACE ([0,100] FOR RATE CONSTANTS AND [-100, 100] FOR KINETIC ORDERS) WITH A BAD INITIAL START (80 FOR ALL PARAMETERS).

|            | variable | $\alpha_i$    | $\beta_j$     | $g_{i1}$      | $g_{i2}$      | $g_{i3}$       | $g_{i4}$ | $h_{i1}$      | $h_{i2}$      | $h_{i3}$      | $h_{i4}$      |
|------------|----------|---------------|---------------|---------------|---------------|----------------|----------|---------------|---------------|---------------|---------------|
| true       | $x_1$    | 20            | 10            |               |               | -0.8           |          | 0.5           |               |               |               |
|            | $x_2$    | 8             | 3             | 0.5           |               |                |          |               | 0.75          |               |               |
|            | $x_3$    | 3             | 5             |               | 0.75          |                |          |               |               | 0.5           | 0.2           |
|            | $x_4$    | 2             | 6             | 0.5           |               |                |          |               |               |               | 0.8           |
| simulation | $x_1$    | 1.9999989E+01 | 9.9999958E+00 |               |               | -8.0000019E-01 |          | 5.0000052E-01 |               |               |               |
|            | $x_2$    | 8.0000209E+00 | 3.0000138E+00 | 4.9999904E-01 |               |                |          |               | 7.4999850E-01 |               |               |
|            | $x_3$    | 3.0000177E+00 | 5.0000229E+00 |               | 7.4999749E-01 |                |          |               |               | 4.9999817E-01 | 1.9999947E-01 |
|            | $x_4$    | 2.0000175E+00 | 6.0000235E+00 | 4.9999784E-01 |               |                |          |               |               |               | 7.9999658E-01 |

### Small-Scale Genetic Network

We further consider a small-scale genetic network, as shown in Fig. 5 (Kikuchi et al., 2003; Hlavacek and Savageau, 1996). The diagram shows that the transcription of the gene  $x_6$  is regulated by two feedback signals from  $x_3$  and  $x_4$ , respectively. The following is the respective S-system:

$$\begin{aligned} \dot{x}_1 &= \alpha_1 x_3^{g_{13}} x_5^{g_{15}} x_6 - \beta_1 x_1^{h_{11}}, \\ \dot{x}_2 &= \alpha_2 x_1^{g_{21}} x_7 - \beta_2 x_2^{h_{22}}, \\ \dot{x}_3 &= \alpha_3 x_2^{g_{32}} x_8 - \beta_3 x_2^{h_{32}} x_3^{h_{33}}, \\ \dot{x}_4 &= \alpha_4 x_3^{g_{43}} x_5^{g_{45}} x_6 - \beta_4 x_4^{h_{44}}, \\ \dot{x}_5 &= \alpha_5 x_4^{g_{54}} x_7 - \beta_5 x_5^{h_{55}}. \end{aligned} \quad (8)$$

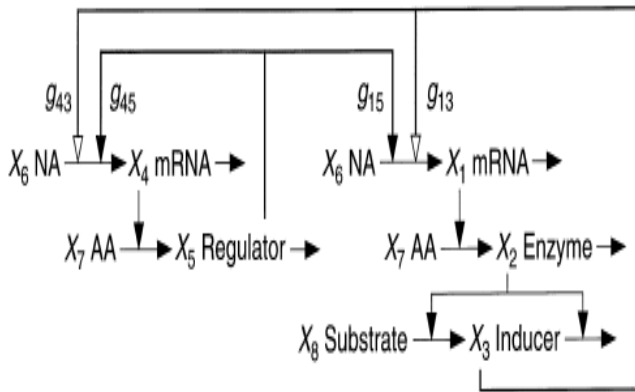


FIG. 5 A SMALL-SCALE GENETIC NETWORK (KIKUCHI ET AL., 2003; HLAVACEK AND SAVAGEAU, 1996)

There are five dependent variables  $x_i$ ,  $i=1, \dots, 5$  and three independent variables  $x_i$ ,  $i=6, 7, 8$ . The values of the rate constants and kinetic orders are listed in Row "True" of Table 3. We generated the same numbers of data sets as the first and second systems. Eight-set artificially experimental data  $x_{\text{exp},i}^i, i=1, \dots, n$ , were generated from the S-type dynamic system. The same technology was used to get the smoothing profiles of these eight-set data sets. Artificial experiments were proceeded from the time-instant  $t=0$  to  $t=0.5$  sec. with a sampling time 0.0125. The estimated parameters are shown in Row "Simulation" of Table 3. The mean-squared error in Eq. (5) is  $9.3606730\text{E-}10$ .

### Medium-Scale Genetic Network

Finally, we consider a twenty-dimensional system, as shown in Fig. 6. The medium-scale genetic network was used by Noman and Iba (2006). The system has twenty dependent variables  $x_i$ ,  $i=1, \dots, 20$ , but not an

independent variables exists in the system. The degradation rate (the efflux  $V_i^-$ ) of each constitute ( $x_i$ ) depends only on himself, which is drawn as the self-feedback signal, as shown in Fig. 6). The regular signals are denoted by the directed branches. From the diagram, we know that the production rate of the constitute  $x_7$  depends on  $x_2$ ,  $x_3$  and  $x_{10}$ . The respective S-system is

$$\begin{aligned} \dot{x}_1 &= \alpha_1 - \beta_1 x_1^{h_{1,1}} & \dot{x}_{11} &= \alpha_{11} x_7^{g_{11,7}} - \beta_{11} x_{11}^{h_{11,11}} \\ \dot{x}_2 &= \alpha_2 - \beta_2 x_2^{h_{2,2}} & \dot{x}_{12} &= \alpha_{12} x_1^{g_{12,1}} - \beta_{12} x_{12}^{h_{12,12}} \\ \dot{x}_3 &= \alpha_3 x_1^{g_{3,15}} - \beta_3 x_3^{h_{3,3}} & \dot{x}_{13} &= \alpha_{13} x_{10}^{g_{13,10}} x_{17}^{g_{13,17}} - \beta_{13} x_{13}^{h_{13,13}} \\ \dot{x}_4 &= \alpha_4 - \beta_4 x_4^{h_{4,4}} & \dot{x}_{14} &= \alpha_{14} x_{11}^{g_{14,11}} - \beta_{14} x_{14}^{h_{14,14}} \\ \dot{x}_5 &= \alpha_5 x_1^{g_{5,1}} - \beta_5 x_5^{h_{5,5}} & \dot{x}_{15} &= \alpha_{15} x_8^{g_{15,8}} x_{11}^{g_{15,11}} x_{18}^{g_{15,18}} - \beta_{15} x_{15}^{h_{15,15}} \\ \dot{x}_6 &= \alpha_6 x_1^{g_{6,1}} - \beta_6 x_6^{h_{6,6}} & \dot{x}_{16} &= \alpha_{16} x_{12}^{g_{16,12}} - \beta_{16} x_{16}^{h_{16,16}} \\ \dot{x}_7 &= \alpha_7 x_2^{g_{7,2}} x_3^{g_{7,3}} x_{10}^{g_{7,10}} - \beta_7 x_7^{h_{7,7}} & \dot{x}_{17} &= \alpha_{17} x_{13}^{g_{17,13}} - \beta_{17} x_{17}^{h_{17,17}} \\ \dot{x}_8 &= \alpha_8 x_3^{g_{8,3}} - \beta_8 x_8^{h_{8,8}} & \dot{x}_{18} &= \alpha_{18} x_{14}^{g_{18,14}} - \beta_{18} x_{18}^{h_{18,18}} \\ \dot{x}_9 &= \alpha_9 x_4^{g_{9,4}} x_5^{g_{9,5}} - \beta_9 x_9^{h_{9,9}} & \dot{x}_{19} &= \alpha_{19} x_{12}^{g_{19,12}} x_{17}^{g_{19,17}} - \beta_{19} x_{19}^{h_{19,19}} \\ \dot{x}_{10} &= \alpha_{10} x_6^{g_{10,6}} x_{14}^{g_{10,14}} - \beta_{10} x_{10}^{h_{10,10}} & \dot{x}_{20} &= \alpha_{20} x_{14}^{g_{20,14}} x_{17}^{g_{20,17}} - \beta_{20} x_{20}^{h_{20,20}}. \end{aligned} \quad (10)$$

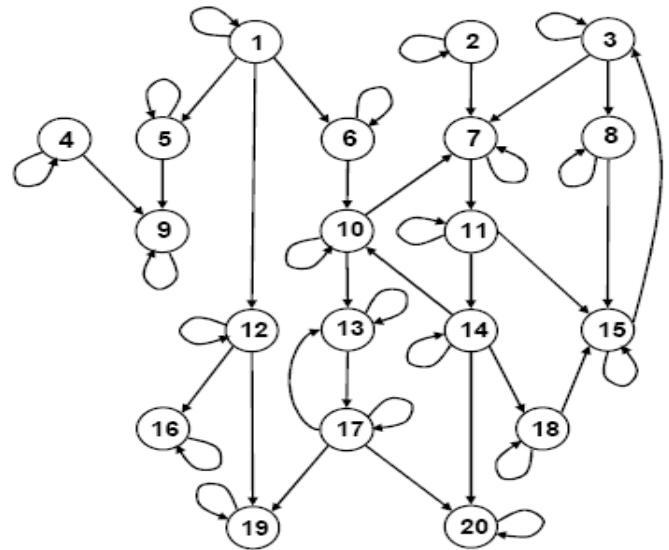


FIG. 6 A MEDIUM-SCALE ARTIFICIAL GENETIC NETWORK (NOMAN AND IBA, 2006)

The rate constants and kinetic orders are listed in Column "True" of Table 4. Eight sets of artificially experimental data ( $x_{\text{exp},i}^i, i=1, \dots, n$ ) were generated. The simulation time is 1.8 seconds and the sampling time is 0.01. The estimated parameters are shown in Column "Simulation" of Table 3. The mean-squared error in Eq. (5) is  $3.5860070\text{E-}08$ .

TABLE 3 TRUE AND ESTIMATED PARAMETERS OF AN S-TYPE SYSTEM FOR A SMALL-SCALE GENETIC NETWORK (5 GENES) IN FIG. 5. ROW "TRUE" IS THE PARAMETERS OF A TRUE S-SYSTEM. ROW "SIMULATION" IS THE ESTIMATED PARAMETERS FOR A WIDE SEARCH SPACE ([0,100] FOR RATE CONSTANTS AND [-100, 100] FOR KINETIC ORDERS) WITH A BAD INITIAL START (80 FOR ALL PARAMETERS).

|                   | variable | $\alpha_i$    | $g_{i1}$      | $g_{i2}$       | $g_{i3}$      | $g_{i4}$      | $g_{i5}$       |
|-------------------|----------|---------------|---------------|----------------|---------------|---------------|----------------|
| <b>true</b>       | $x_1$    | 5             |               |                | 1             |               | -1             |
|                   | $x_2$    | 10            | 2             |                |               |               |                |
|                   | $x_3$    | 10            |               | -1             |               |               |                |
|                   | $x_4$    | 8             |               |                | 2             |               | -1             |
|                   | $x_5$    | 10            |               |                |               | 2             |                |
| <b>simulation</b> | $x_1$    | 5.0001303E+00 |               |                | 9.9998968E-01 |               | -9.9995275E-01 |
|                   | $x_2$    | 1.0001287E+01 | 2.0002720E+00 |                |               |               |                |
|                   | $x_3$    | 1.0000504E+01 |               | -9.9997306E-01 |               |               |                |
|                   | $x_4$    | 7.9994667E+00 |               |                | 2.0000315E+00 |               | -1.0000379E+00 |
|                   | $x_5$    | 9.9998524E+00 |               |                |               | 1.9999180E+00 |                |
|                   |          |               |               |                |               |               |                |
|                   | Variable | $\beta_i$     | $h_{i1}$      | $h_{i2}$       | $h_{i3}$      | $h_{i4}$      | $h_{i5}$       |
| <b>true</b>       | $x_1$    | 10            | 2             |                |               |               |                |
|                   | $x_2$    | 10            |               | 2              |               |               |                |
|                   | $x_3$    | 10            |               | -1             | 2             |               |                |
|                   | $x_4$    | 10            |               |                |               | 2             |                |
|                   | $x_5$    | 10            |               |                |               |               | 2              |
| <b>simulation</b> | $x_1$    | 1.0000254E+01 | 2.0000300E+00 |                |               |               |                |
|                   | $x_2$    | 1.0001098E+01 |               | 2.0001249E+00  |               |               |                |
|                   | $x_3$    | 1.0000554E+01 |               | -9.9996751E-01 | 1.9999823E+00 |               |                |
|                   | $x_4$    | 9.9994108E+00 |               |                |               | 2.0001029E+00 |                |
|                   | $x_5$    | 9.9997759E+00 |               |                |               |               | 1.9999322E+00  |

TABLE 4 TRUE AND ESTIMATED PARAMETERS OF AN S-TYPE SYSTEM FOR A MEDIUM-SCALE GENETIC NETWORK (20 GENES) IN FIG. 6. "TRUE" IS THE PARAMETERS OF A TRUE S-SYSTEM. "SIMULATION" IS THE ESTIMATED PARAMETERS FOR A WIDE SEARCH SPACE ([0,100] FOR RATE CONSTANTS AND [-100, 100] FOR KINETIC ORDERS) WITH A BAD INITIAL START (80 FOR ALL PARAMETERS).

| Variable | $\alpha_i$ |               | $\beta_j$ |               | $g_{ij}$    |      |                |             |      |                |             |             | $h_{ij}$        |  |
|----------|------------|---------------|-----------|---------------|-------------|------|----------------|-------------|------|----------------|-------------|-------------|-----------------|--|
|          | True       | Simulation    | True      | Simulation    |             | True | Simulation     |             | True | Simulation     |             | True        | Simulation      |  |
| $x_1$    | 10         | 1.0000297E+01 | 10        | 1.0000305E+01 |             |      |                |             |      |                |             | $h_{1,1}$   | 1 9.9995360E-01 |  |
| $x_2$    | 10         | 9.9967434E+00 | 10        | 9.9967500E+00 |             |      |                |             |      |                |             | $h_{2,2}$   | 1 1.0002619E+00 |  |
| $x_3$    | 10         | 9.9844220E+00 | 10        | 9.9846528E+00 | $g_{3,15}$  | -0.7 | -7.0103210E-01 |             |      |                |             | $h_{3,3}$   | 1 1.0011089E+00 |  |
| $x_4$    | 10         | 9.9944492E+00 | 10        | 9.9943897E+00 |             |      |                |             |      |                |             | $h_{4,4}$   | 1 1.0005457E+00 |  |
| $x_5$    | 10         | 9.9998308E+00 | 10        | 9.9998242E+00 | $g_{5,1}$   | 1    | 1.0000215E+00  |             |      |                |             | $h_{5,5}$   | 1 1.0000262E+00 |  |
| $x_6$    | 10         | 9.9915335E+00 | 10        | 9.9914074E+00 | $g_{6,1}$   | 2    | 2.0009461E+00  |             |      |                |             | $h_{6,6}$   | 1 1.0006176E+00 |  |
| $x_7$    | 10         | 1.0004115E+01 | 10        | 1.0004090E+01 | $g_{7,2}$   | 1.2  | 1.1995465E+00  | $g_{7,3}$   | -0.8 | -7.9951086E-01 | $g_{7,10}$  | 1.6         | 1.5995012E+00   |  |
| $x_8$    | 10         | 9.9992851E+00 | 10        | 9.9994738E+00 | $g_{8,3}$   | -0.6 | -5.9989812E-01 |             |      |                |             | $h_{7,7}$   | 1 9.9962616E-01 |  |
| $x_9$    | 10         | 9.9926937E+00 | 10        | 9.9926915E+00 | $g_{9,4}$   | 0.5  | 5.0033430E-01  | $g_{9,5}$   | 0.7  | 7.0040388E-01  |             | $h_{8,8}$   | 1 1.0001681E+00 |  |
| $x_{10}$ | 10         | 9.9921722E+00 | 10        | 9.9921528E+00 | $g_{10,6}$  | -0.3 | -3.0024507E-01 | $g_{10,14}$ | 0.9  | 9.0058533E-01  |             | $h_{9,9}$   | 1 1.0006036E+00 |  |
| $x_{11}$ | 10         | 9.9972180E+00 | 10        | 9.9972245E+00 | $g_{11,7}$  | 0.5  | 5.0004952E-01  |             |      |                |             | $h_{10,10}$ | 1 1.0007662E+00 |  |
| $x_{12}$ | 10         | 9.9994790E+00 | 10        | 9.9994673E+00 | $g_{12,1}$  | 1    | 1.0000685E+00  |             |      |                |             | $h_{11,11}$ | 1 1.0001809E+00 |  |
| $x_{13}$ | 10         | 9.9931863E+00 | 10        | 9.9931204E+00 | $g_{13,10}$ | -0.4 | -4.0024791E-01 | $g_{13,17}$ | 1.3  | 1.3006565E+00  |             | $h_{12,12}$ | 1 1.0000304E+00 |  |
| $x_{14}$ | 10         | 9.9949074E+00 | 10        | 9.9949011E+00 | $g_{14,11}$ | -0.4 | -4.0016743E-01 |             |      |                |             | $h_{13,13}$ | 1 1.0006807E+00 |  |
| $x_{15}$ | 10         | 1.0014626E+01 | 10        | 1.0014522E+01 | $g_{15,8}$  | 0.5  | 4.9936163E-01  | $g_{15,11}$ | -1   | -9.9883731E-01 | $g_{15,18}$ | -0.9        | -8.9869073E-01  |  |
| $x_{16}$ | 10         | 9.9935604E+00 | 10        | 9.9935719E+00 | $g_{16,12}$ | 2    | 2.0007375E+00  |             |      |                |             | $h_{14,14}$ | 1 1.0004572E+00 |  |
| $x_{17}$ | 10         | 1.0009306E+01 | 10        | 1.0009349E+01 | $g_{17,13}$ | -0.5 | -4.9959075E-01 |             |      |                |             | $h_{15,15}$ | 1 9.9870315E-01 |  |
| $x_{18}$ | 10         | 9.9916051E+00 | 10        | 9.9913900E+00 | $g_{18,14}$ | 1.2  | 1.2009002E+00  |             |      |                |             | $h_{16,16}$ | 1 1.0004371E+00 |  |
| $x_{19}$ | 10         | 9.9962350E+00 | 10        | 9.9962400E+00 | $g_{19,12}$ | 1.4  | 1.4003111E+00  | $g_{19,17}$ | 0.6  | 6.0005863E-01  |             | $h_{17,17}$ | 1 9.9907814E-01 |  |
| $x_{20}$ | 10         | 1.0002587E+01 | 10        | 1.0002497E+01 | $g_{20,14}$ | 1    | 9.9986162E-01  | $g_{20,17}$ | 1.5  | 1.4996378E+00  |             | $h_{18,18}$ | 1 1.0009199E+00 |  |
|          |            |               |           |               |             |      |                |             |      |                |             | $h_{19,19}$ | 1 1.0002798E+00 |  |
|          |            |               |           |               |             |      |                |             |      |                |             | $h_{20,20}$ | 1 9.9983425E-01 |  |

## Discussion

Learning in the wide range and the bad initial start is to show that the exploratory ability of the gradient-based method is largely increased. We observed that the proposed technology is able to escape from local minima and keeps the advantage of computation time. The results of Tables 1-4 show the high accuracy of the proposed method. The mean-square error in Eq. (5) is  $1.0591741\text{E-}10$  for 3-gene,  $2.2096583\text{E-}11$  for 4-gene,  $9.3606730\text{E-}10$  for 5-gene, and  $3.5860070\text{E-}08$  for 20-gen systems.

We further use Figs. 7-10 to show the advantage of convergence. We observe that most of the curves converge at around 1000 fitness evaluation. In addition to the strongly nonlinearity, biological systems are always stochastic wherein the time-series data are heavy noisy. Therefore, we further consider the artificial data with 10% random noise. Fig. 11 shows that the proposed method is able to predict the dynamic behaviour of the system even in a noisy environment. The results are comparable to Fig. 4 of Sriyudthask's paper (2013) where 0 to 5% noisy data are used.

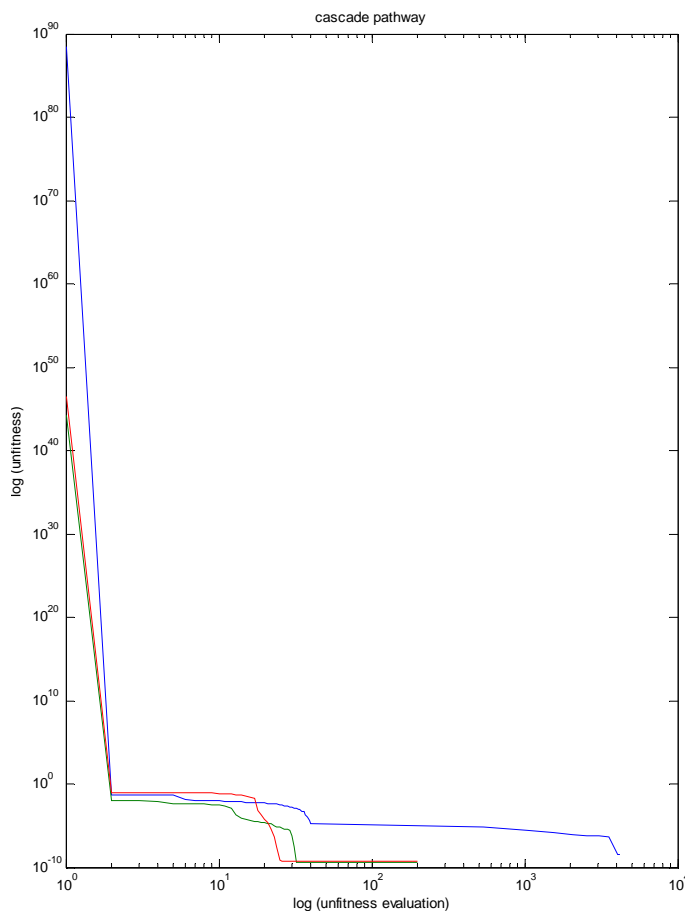


FIG. 7 THE CONVERGENCE OF THE PROPOSED METHOD APPLIED TO THE CASCADE-PATHWAY SYSTEM IN EQ. (6).

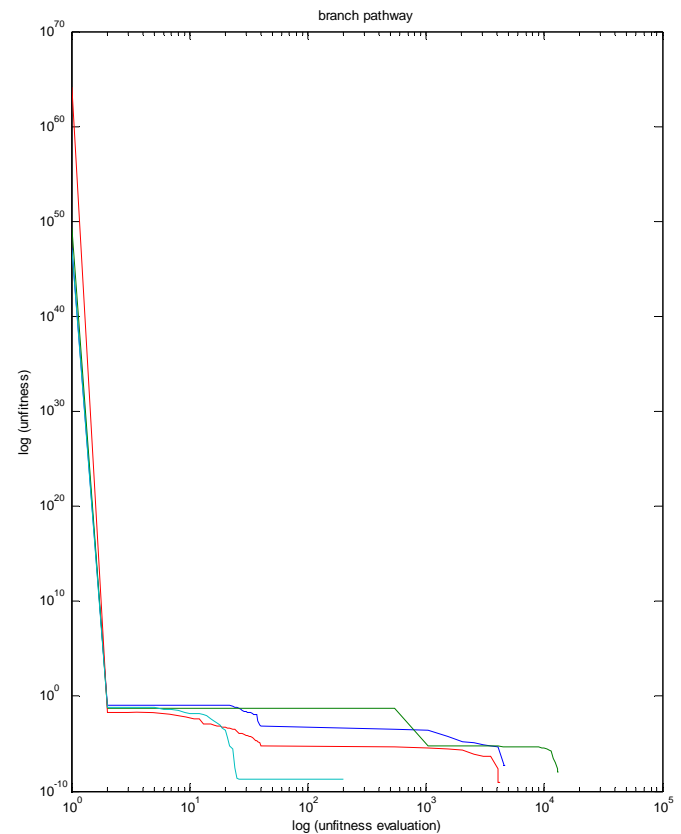


FIG. 8 THE CONVERGENCE OF THE PROPOSED METHOD APPLIED TO THE GENETIC-BRANCH PATHWAY IN EQ. (7).

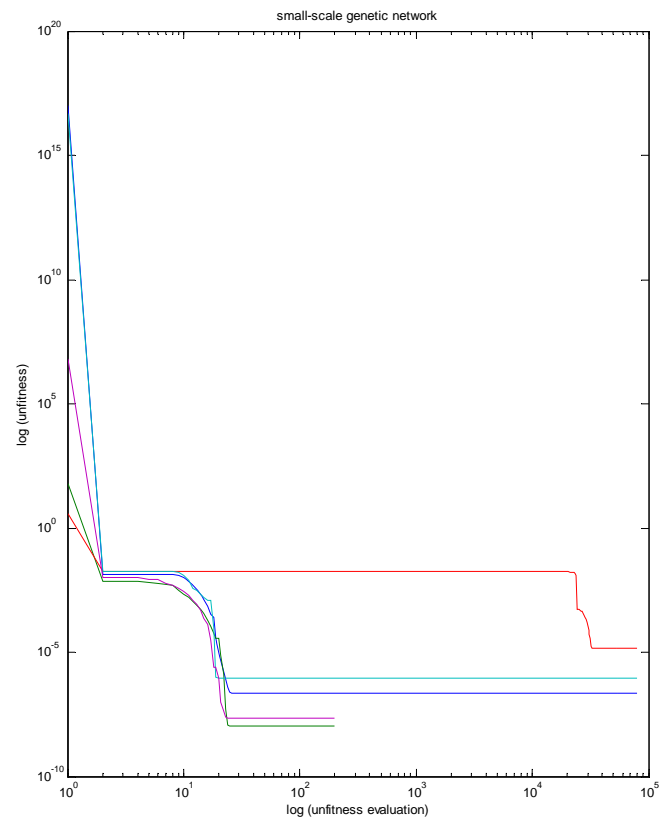


FIG. 9 THE CONVERGENCE OF THE PROPOSED METHOD APPLIED TO THE SMALL-SCALE GENETIC NETWORK IN EQ. (8).



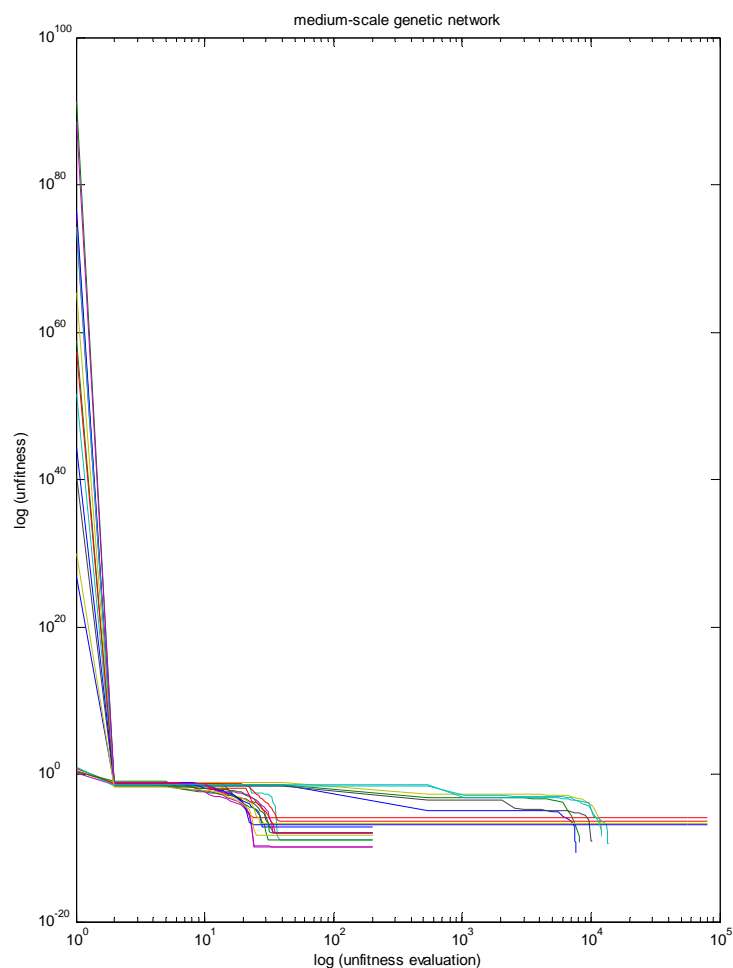


FIG. 10 THE CONVERGENCE OF THE PROPOSED METHOD APPLIED TO THE MEDIUM-SCALE ARTIFICIAL GENETIC NETWORK IN EQ. (9).

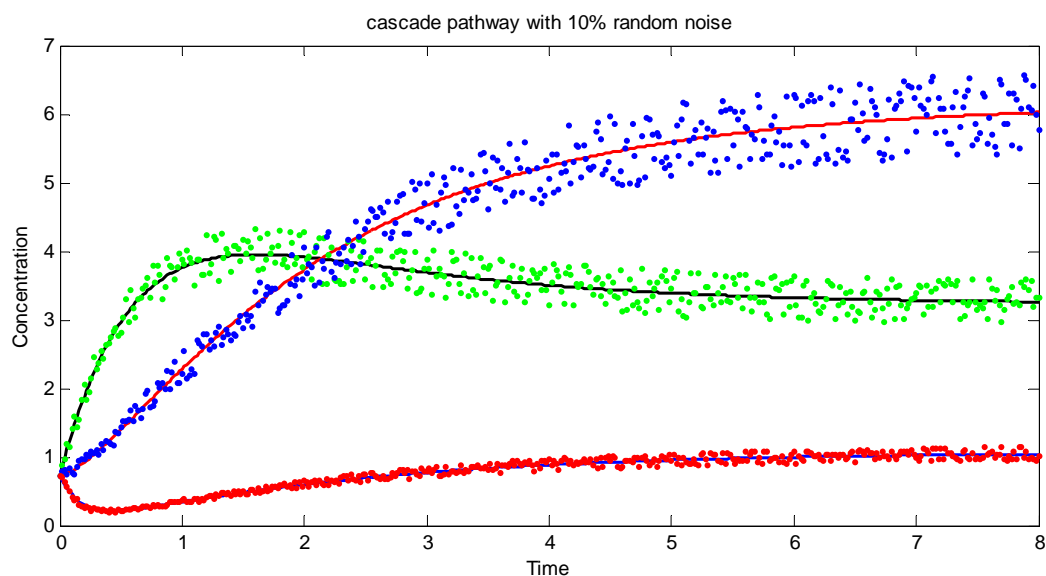


FIG. 11 ROBUST EXAMINATION FOR THE GRADIENT-BASED METAHEURISTICS OPTIMIZATION IN THE CASCADE-PATHWAY. DOT POINTS ARE DATA WITH 10% RANDOM-NOISE CONTAMINATE. SOLID CURVES ARE THE ESTIMATED PROFILES. A WIDE SEARCH SPACE  $([0, 100])$  FOR RATE CONSTANTS AND  $[-100, 100]$  FOR KINETIC ORDERS) AND A BAD INITIAL START (80-NEIGHBORHOOD FOR ALL PARAMETERS) ARE USED. INITIAL CONDITIONS ARE 20% BEYOND THE TRAINING RANGE.

## Conclusions

Identifying a dynamic biological system from time-series data is a central theme in systems biology. S-systems are demonstrated to be a good approximation of smooth nonlinear systems. However, the parameter identification of S-systems is challenging because the S-system is described as coupled highly nonlinear differential equations. How to make a trade-off between the accuracy (reliability) and computation time is important. Instead of improving the local-search ability of the population-based computational methods, we propose an inverse aspect: The incorporation of stochastic-search operations (migration synchronous evolution) into traditional gradient-based optimizers. The synchronous mutation is to increase the population diversity and the migration operation to widen the searching. The simulation results exhibit that the proposed scheme is able to escape from local minima in a reasonable computation cost, even the dimension of the system is as high as 20 and the searching space is wide.

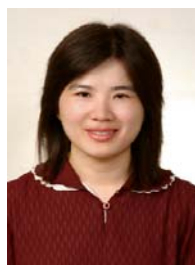
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